and prostaglandins the tonic component of the contraction is substantially activated, which negatively affects the condition of the intrauterine fetus. Apparently, to judge from their chemical structures, the compounds that we have studied possess a double mechanism of action, ganglioblocking and beta-adrenoblocking. However, their beta-adrenoblocking properties are less pronounced than with anapriline; when they are administered intravenously, the arterial pressure is not lowered and there is only a temporary reaction on the injection, which lasts 30-60 sec, after which the arterial pressure is restored to the initial value; in that case the frequency of heart contractions does not change substantially.

The data that we have obtained point to the advisability of further synthesis and investigation of uterostimulating properties of derivatives of 1-dialkylamino-3-alkoxy-2-propanol to identify potential pharmacological compounds that stimulate the contracting function of the uterus.

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SYNTHESIS AND BIOLOGICAL ACTIVITIES OF SOME AMIDES OF 2-OXO-1-OXAPYRO[4,5]DECANE-4-CARBOXYLIC ACIDS

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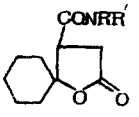
Until now quite a large number of derivatives of γ-lactones have been synthesized and their biological activities have been studied [5]. At the same time there still is the problem of synthesis and biological activities of derivatives of spirolactones, which, in our opinion, is connected with the lack of practicable methods for the synthesis of these compounds.

During our investigations into the synthesis of potential biologically active compounds of the group of derivatives of spirolactones and the establishment of the structure-activity relationship, starting from 2-oxo-1-oxaspiro[4,5]decane-4-carboxylic acids (I) [1] we have prepared acid chloride II, which on reaction with primary and secondary amines in benzene yields amides of 2-oxo-1-oxaspiro[4,5]decane-4-carboxylic acid (IIIa-f). We have studied the biological activities of the latter.



IIIa-f

R=H (IIIa-c), CH_3 (IIId), C_2H_5 (IIIe); R'=H (IIIa), C_6H_5 (IIIb), $CH_2C_6H_5$ (IIIc), CH_3 (IIId), C_2H_5 (IIIe); NRR'= morpholino (IIIf)

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TABLE 1. Amides of 2-Oxo-1-oxaspiro[4,5]-decane-4-carboxylic Acid IIIa-f

Compound	Yield, %	R_f	mp, °C (solvent)	Empirical formula
IIIa	83	0,45*	200 (ethanol–water)	$C_{10}H_{15}NO_3$
IIIb	80	0,5**	198 (ethanol)	$C_{16}H_{19}NO_3$
IIIc	87	0,55**	146 (ethanol)	$C_{17}H_{21}NO_3$
IIId	70	0,53**	102 (ethanol–water)	$C_{12}H_{19}NO_3$
IIIe	65	0,63**	88—90 (ethanol)	$C_{14}H_{23}NO_3$
IIIf	73	0,47**	131—132 (ethanol–water)	$C_{14}H_{21}NO_4$

*Chloroform–acetone, 6:4.
**Chloroform–acetone, 8:2.
***Chloroform–acetone, 7:3.

TABLE 2. Spectra of Compounds IIIa-f

Compound	IR spectrum, ν, cm^{-1}				PMR spectrum, δ, ppm (solvent)	Mass spectrum, m/z (intensity, %)
	arom.	C=O amide	C=O lact.	NH		
IIIa	–	1660	1770	3200 3420	(DMCOD$_6$) 1,20—1,90 (10H, m, 6, 7, 8, 9, 10-CH_2); 2,6—2,75 (2H, m, 3-CH_2); 3,10 (1H, dd, 4-CH)	197 (95,2), 138 (38,1), 99 (100)
IIIb	1600	1670	1780	3380	(P_y-D_6) 1,00—2,20 (10H, m, 6, 7, 8, 9, 10-CH_2); 2,66—3,50 (3H, m, 3-CH_2 and 4-CH); 6,90—8,10 (6H, m, PhNH).	273 (40), 214 (11,2), 152 (100), 93 (55,6)
IIIc	1575	1640	1770	3290	(DMCOD$_6$) 1,10—1,80 (10H, m, 6, 7, 8, 9, 10-CH_2); 2,66—3,20 (3H, m, 3-CH_2 and 4-CH); 4,33 (2H, d, NH-$\underline{CH_2}$); 7,30 (5H, s, Ph); 8,65 (1H, t, NH).	287 (80), 269 (2), 228 (100), 189 (30), 162 (44), 106 (70), 91 (64), 55 (50).
IIId	–	1640	1780		(CDCl$_3$) 1,00—2,00 (10H, m, 6, 7, 8, 9, 10-CH_2); 2,86 (3H, s, N-CH_3); 3,00 (3H, s, N-CH_3); 2,45—2,80 (2H, m, 3-CH_2); 3,40 (1H, dd, 4-CH).	225 (25,3), 197 (25,3), 182 (22), 167 (2,3), 166 (28,7), 165 (91,7), 128 (33,3), 127 (27,6), 126 (2,3), 100 (28,7), 98 (57,4), 87 (23), 72 (100), 55 (57,4), 44 (51,7).
IIIe	–	1640	1770		(CDCl$_3$) 1,10 3H, t, CH_3); 1,17 (3H, t, CH_3); 1,20—2,20 (10H, m, 6, 7, 8, 9, 10-CH_2); 2,50—4,00 (7H, m, 3-CH_2, 4-CH, 4-$\underline{CH_2}$—CH_3)	253 (90,9), 225 (54,5), 210 (36,4), 209 (27,3), 194 (100), 155 (54,5).
IIIf	–	1640	1770		(CDCl$_3$) 1,20—2,20 (10H, m, 6, 7, 8, 9, 10-CH_2); 2,40—3,35 (2H, m, 3-CH_2); 3,50 (1H, dd, 4CH); 3,70 (8H, m, N, ($\underline{CH_2}\underline{CH_2}$)$_2$O).	267 (17), 249 (1,4), 239 (7), 223 (2,8), 208 (100), 169 (59,8), 142 (55,6), 129 (8,4), 114 (30,5), 87 (41,6), 70 (27,7), 57 (55,5).

The structures of amides IIIa-f were confirmed by IR, PMR, and mass spectrometry (Tables 1 and 2).

EXPERIMENTAL (CHEMICAL)

IR spectra were taken on a UR-20 spectrometer in paraffin oil. PMR spectra were recorded on a Varian T-60 spectrometer (USA) operating at 60 MHz. TLC was carried out on Silufol UV-254 plates (Czechoslovakia), spots were visualized in iodine vapour. Data of elemental analyses were in agreement with calculated values.

2-Oxo-1-oxaspiro[4,5]decane-4-carboxyl Chloride (II). A suspension of 19.8 g (0.1 mole) of 2-oxo-1-oxospiro[4,5]decane-4-carboxylic acid [1] in 200 ml of absolute benzene and 17.8 g (0.15 mole) of thionyl chloride is refluxed for 6 h. Benzene and excess of thionyl chloride are distilled off at reduced pressure, to the residue is added twice 70 ml of absolute benzene, which each time is distilled off. The residue is distilled under vacuum. Yield 18.5 g of compound II (93.53), bp 168-171°C/3 mm. PMR spectrum (CDCl$_3$), δ, ppm: 1.13-2.36 m (10H, 6,7,-8,9,10-CH_2), 2.73 d (2H, d, 3-CH_2), 3.36-3.83 m (1H, m, 4-CH).

2-Oxo-1-oxaspiro[4,5]decane-4-carboxamides (IIIa-f). To a solution of 0.08 mole of the appropriate amine in 100 ml of absolute benzene is added in 1-1.5 h dropwise with stirring 8.66 g (0.04 mole) of II in 150 ml of benzene. The reaction mixture is heated at 60°C for 1-2 h, cooled, 50 ml of water is added, and the mixture is extracted with ether or benzene. The organic layer is extracted with 10% HCl solution, water, 10% sodium carbonate solution, and dried over magnesium sulfate. The solvent is evaporated and the residue is crystallized from the appropriate solvent (see Tables 1 and 2).

TABLE 3. Toxicity and Antitumor Activity of Compounds I, IIIa-f

Compound	LD_{100} in mg/kg (mice)	MED	Dose, mg/kg per day	Sarcoma		Pliss' lymphosarcoma		Dose, mg/kg per day	Sarcoma 37		Ehrlich's ascitic carcinoma	Sarcoma 180	
				T%	Kp. %	T%	Kp. %		T %	Kp. %	ILS %	T %	Kp. %
I	3000	2500	150	48*	−12	0		250	32*	+1,3			
IIIa	2500	2000	120	Stimul.		35	+1,5	200	28*	+13			
IIIb	2750	2000	135	22*	+9,3	20,6*	−3,3		--				
IIIc	5000	—	250	54	−1,3	47	−2,5	500	0			51	+2,0
IIId	500	400	20	66	+5,9	0		50	0			48	−3,3
IIIe	650	400	30	21*	+10,1	0			–	Inactive			
IIIf	1100	80	50	0		0							
5-Fluorouracil	200	75	10	32	−7,3	41	−6,4	25	7	−9,2	39	46	46–11

*Uncertain ($\alpha < 0.95$).

EXPERIMENTAL (BIOLOGICAL)

We have studied the antitumor, psychotropic, and antiarrhythmic activities of the amides of 2-oxo-1-oxaspiro[4,5]decane-4-carboxylic acid.

Chemotherapeutic experiments were carried out according to a method described earlier [4] with white mongrel rats (weighing 90-120 g) and mice (weighing 18-21 g) of both sexes.

The acute toxicity (LD_{100} and MED) of compounds I and IIIa-f was determined by single intraperitoneal administration to mice. Study of their antitumor activity was carried out with entwined tumors of rats with sarcoma 45 and Pliss' lymphosarcoma, and mice with sarcoma 37 and Ehrlich's ascitic carcinoma. The effectivity of comparatively active compounds was also determined in mice with sarcoma 180. The compounds were administered to the animals intraperitoneally as suspensions in a 0.5% solution of carboxymethylcellulose (I, IIId) or an isotonic sodium chloride solution (IIIa-c, e, f). The therapeutic effect of the compounds was judged by the percentage of inhibition of solid tumors (T%) or the increase in life span of the mice (ILS, %) in comparison with the control. The results of the experiments were compared with data of the antimetabolite 5-fluorouracil; they are listed in Table 3.

In experiments with mice we studied the effect of compounds I, IIId, and IIIf on the motor activity and also the effect on the soporific action of hexenal and on the toxicity of tryptamine in grouped mice [2]. In experiments in vitro we investigated the effect of the compounds on the monoamine oxidase (MAO) activity in reference to serotonin (5-OT). The MAO activity was determined in 50% homogenates of rat brain [3]. The compounds under investigation were administered subcutaneously (s.c.) at doses of 50 and 100 mg/kg. Hexenal (70 mg/kg) and tryptamine (250 mg/kg) were administered intraperitoneally one hour after injection of the compound. In experiments in vitro the compounds were tested in concentrations of 1 μmole/ml of sample.

The antiarrhythmic activity of compounds IIId and IIIf was studied according to method [6].

Experimental data were processed statistically according to Student-Fisher, reliable at $\alpha \geq 0.95$ or $p \leq 0.05$.

Study of the acute toxicity (see Table 3) showed that compounds IIId, e are relatively toxic; in the case of intraperitoneal administration to mice their LD_{100} is 500-600 mg/kg, the MED is 400 mg/kg. The other compounds are little toxic: their LD_{100} varies from 1100 to 3000 and 5000 mg/kg, their MED from 80 to 2500 mg/kg. However, all the amides studied are less toxic than 5-fluorouracil.

The results of the chemotherapeutic experiments (see Table 3) showed that two compounds have a certain effect on sarcoma 45 at therapeutic doses. Of them the amide with a benzyl radical (IIIc) showed moderate activity (T = 54%, $\alpha > 0.95$). The amide with a dimethylcarbamoyl radical (IIId) has noticeable antitumor action on the tumor mentioned (T = 66%, $\alpha > 0.99$) and does not show a toxic effect on the organism of the experimental rats.

With respect to the growth of Pliss' lymphosarcoma, amides IIIa and IIIc, in contrast to acid I, proved to be of low activity. On treatment of mice with sarcoma 37 and Ehrlich's ascitic carcinoma a reliable activity was not found.

The most active amides, IIIc and IIId, were tested with respect to sarcoma 180. These compounds showed moderate antitumor activity by inhibiting its growth by 48-51% ($\alpha > 0.95$) and did not show toxic effects on the organism of the experimental rats.

Thus, the antitumor effect that we have found (compounds IIIc, d) shows promise for carrying out further search among amides of 2-oxo-1-oxaspiro[4,5]decane-4-carboxylic acid.

Investigation of the psychotropic properties of compounds I, IIId, and IIIf showed that they cause some oppression of the motor activity in mice. Given at a dose of 100 mg/kg, the compounds prolong the soporific effect of hexenal almost two times ($p < 0.05$) and essentially do not affect the toxicity of tryptamine.

In experiments in vitro the compounds under investigation have weak antimonoamine oxidase activity (20-25%).

During investigation of compounds IIIe-f with the experimental model of arrhythmia of the heart it was found that at doses of 3-5 mg/kg they possess antiarrhythmic activity and a noticeable effect on the arterial pressure and the frequency of heart contractions.

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SYNTHESIS AND PROPERTIES OF 1,4-BENZODIKETO- AND 1,4-BENZOMONO KETODICARBOXYLIC ACIDS AND THEIR DERIVATIVES

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Alkyl- and arylglyoxylic acids are important intermediates in the metabolism and biosynthesis of many natural amino acids, and, because of the presence of highly reactive groupings, they are also widely used in the syntheses of heterocyclic and other organic compounds. Data on the known methods of synthesis and properties of α-ketoacids are presented in reviews [2, 3].

One of the most promising methods of preparation of arylglyoxylic acid is based on the oxidation of ethyl-substituted benzenes by potassium permanganate solutions. It was previously shown that in the oxidation of 1,4-diethylbenzene by $KMnO_4$ in an alkaline medium, a mixture of 1,4-benzenediketodicarboxylic acid (I), 1,4-benzenemonodicarboxylic (II) and terephthalic (III) acids is formed [1].

However, these acids could not be separated into individual components, and their properties, except for III were practically not investigated. It was of interest to obtain them in a pure state and to study the chemical characteristics of the structurally similar compounds I and II.

We have now separated acids I and II from the mixture of oxidation products of p-diethylbenzene for the first time. The free acids were isolated by acidifying the partially evaporated aqueous solutions of potassium salts of the oxidation products with hydrochloric acid to pH 3.0-3.5 and separating the precipitated terephthalic acid III. A mixture of I and II was obtained by extraction from a strongly acidified filtrate with diethyl ether.

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